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gives good hope that the public will have excellent scientific help in the promotion of the national mineral industry.

After the opening ceremony the president, followed by the other guests, made a tour of inspection of the library and of the museum.

H. T. CHANG,
Acting Director

PEKING,
JULY 17, 1922

AGGLUTINATION AND TISSUE FORMATION

FOR a considerable number of years the principle underlying our analysis of tissue formation—undertaken with the view of contributing to a physiology of tissues in contradistinction to a physiology of organs¹—was the suggestion that primarily agglutination is the factor which makes isolated cells join into a tissue, and that this agglutination depends on a certain consistency of the outer layer of the cell protoplasm². In an analysis of tissue formation it was thus necessary to determine the factors on which this consistency depends and we showed that it is a quantitatively variable factor, that this variability is a prerequisite in amoeboid movement and that the same agglutinability which determines tissue formation is the cause of what we have called stereotropism of tissue cells, their tendency to move in contact with solid surfaces.² Tissue formation, stereotropism and amoeboid movement are therefore related phenomena, all depending on a certain variability and regulation in the consistency of the outer layer of the protoplasm. As a step in this investigation we prepared an experimental amoebocyte tissue which consists of motile bloodcells of invertebrates and which readily admits of an experimental analysis of all these associated factors.³ The basic laws of tissue formation must apply

equally to the various kinds of growth, embryonic, regenerative, correlative and tumor growth.⁴

Tissues are primarily aggregates of agglutinated cells. Secondly certain differentiations may occur which concern the individual cells as well as the connections between these cells. Elementary tissues and even structures resembling particular tissues in certain respects, can be produced from isolated amoebocytes under conditions which we have described in detail elsewhere. Under the influence of environmental changes the consistency of the outer protoplasmic layer of these cells is altered in such a way that it becomes sticky. In this experimental tissue various processes which occur in natural tissues can be imitated. A state of the outer parts of the protoplasm intermediate between liquid and solid is essential for tissue formation, because it insures that degree of adhesiveness necessary for this process. Agglutination is likewise the basic factor, which insures the possibility of the formation of paraplasmic structures in which the products of adjoining cells are united into a homogeneous whole.

We showed that the movements of tissue cells take place in contact with surfaces which are solid or approach the solid state, such as fibres. We designated this mode of reaction as stereotropism of tissue cells (1898), and attributed to it a significant part, not only in wound healing, but also in processes taking place normally in the organism whenever movements of tissue cells occur.⁵ This stereotropism is apparent not only in normally motile cells, but even in cells which are normally in a fixed condition but which are made to move under conditions which imply a change in environment; it is self-evident that this includes also those environmental changes which take place during embryonal development. We found that this stereotropic reaction can

¹*Biological Bulletin*, 1903, IV, 1301, Virchow's *Archiv.* 1903, CLXXIII, 135 *Anatomical Record* 1912 VI, 109.

²Washington University studies 1920, VIII, 3. *American Journ. Physiol.* 1921, LVI, 140. *Science* 1921, LIII, 261.

³Washington University Studies, 1920. VIII. 3 *Science* 1919 L. 502. *American Journal Physiol.* 1922, LX, 277.

⁴Virchow's *Archiv.* 1903, CLXXIII, 135. *Journ. Med. Research*, 1917, XXXII, 75, 1920, XLI, 247. *Journ. Cancer Research*, 1920, V, 261. *Science*, 1922, LV, No. 1410.

⁵*Archiv. f. Entwicklungsmech.* 1898, VI, 297. 1902, XIII, 487. *Anatomical Record*, 1912, VI, 109. M. S. Fleischer and Leo Loeb. *Proc. Soc. Exp. Biol. and Med.*, 1911, VIII, 133.

be induced and modified experimentally in the amœbocytes and that it depends upon changes in the consistency of the protoplasm, which tend to make it sticky. Stereotropism is therefore an expression of the same factor which leads to the agglutination of isolated cells with each other, which latter results in tissue formation.

The stereotropism of tissue cells depends upon their ability to carry out amœboid movements. On the basis of our observations and experiments we concluded that in amœboid movements, cyclic changes in the consistency of those parts of the protoplasm take place which are concerned in this activity.⁶ With these changes there must be associated corresponding changes in the agglutinative power of the tissue cells. The factors underlying amœboid movements are therefore closely related to those determining agglutination and tissue formation; but while in the latter usually the whole surface of the cell is in a viscous state, the cyclic changes in consistency and viscosity of the protoplasm are localized and thus lead to the formation of pseudopods. In modifying this amœboid movement experimentally we have shown that its character varies with the consistency of the protoplasm; only if the latter approaches the liquid state can surface tension play a part in the amœboid movement; but during certain phases of the process the consistency of the protoplasm is so great that the laws of surface tension, as they have been defined for the liquid state of matter, cannot play an essential part in amœboid movement.⁷

Related to amœboid movement but not identical with it, is the spreading out of tissue cells, which occurs under certain conditions, when the cells are in contact with solid surfaces. This process can likewise very conveniently be studied in amœbocytes. Both amœboid movement and spreading out depend upon changes in the consistency of the protoplasm. The spreading out in particular depends upon a softening and relaxation of the outer layer of the protoplasm. Usually this spreading out goes hand in hand with amœboid

movement; yet both processes can to a certain extent be separated from each other experimentally. As we have shown, it is possible to increase the consistency of the protoplasm in such a way, that the spreading out is prevented or very much delayed, while amœboid movements are still quite active. Addition of definite amounts of acids to the medium in which the amœbocytes are held, may have this effect. However, in influencing the consistency of the outer layer of the protoplasm as a whole, for instance through the addition of acid, we may also influence the character of the pseudopods in a corresponding manner. Addition of slight amounts of alkali favors very much the extension of the cells by softening the consistency generally.⁸ Again the consistency of the outer layer of the spreading out cell is such that adhesiveness results; thus an agglutination of the spreading out cells to the base on which they rest is assured. This spreading out is an important factor in tissue formation and during embryonic development the formation of the mesenchyme depends upon such a transformation of the more or less rounded off blastomeres into cells, which not only assume amœboid movement, but at the same time spread out. We have previously called attention to the importance of changes in agglutinative properties of cells during embryonic development, in which a change takes place from agglutinated round cells, which stick to each other with certain parts of their circumference, to cells spreading out in contact with a solid or viscous substratum.⁹

It can be shown that the stickiness and therefore the agglutinability of cells is a variable factor; but the degree of this variability differs very much in different kinds of cells and under different conditions. We have found that this variability is very great in the case of amœbocytes. In the circulating blood they are not sticky; but as soon as the environment is altered they become sticky, show amœboid movements and agglutinate to each other and to other structures. We have every reason to believe that, while these variations in stickiness are less marked in the majority

⁶*Journal Med. Research*, 1902, VII, 145.

⁷Washington University Studies, 1920, VIII, 3.

⁸*American Journal Physiol.* 1922, LX, 277.

⁹SCIENCE, 1922, LV, No. 1410.

of cells, great variations occur generally. Thus in the resting stage, the endothelial cells lining blood and lymph vessels present a perfectly smooth surface and other cells pass them freely without adhering to them. But when certain changes in the environment occur, these cells may become amœboid and migrate adhering to surfaces; or they assume phagocytic properties, which likewise presuppose certain changes in the surface consistency. It is very probable that similar changes occur in all epithelial or connective tissue cells, when they change from the resting state to the active state of amœboid migration, adhering to surfaces with which they come in contact. Amœboid movement as such implies, as we have shown, a cyclic, localized change in the consistency of the cell and it can be shown that the stickiness of the pseudopod may be greater than that of the rest of the cell. In the majority of the cells the variation in consistency and stickiness is less marked than in the case of the amœbocytes, because they are already naturally in the state of tissue components, adhering with certain parts of their surface to neighboring cells. This applies already to the blastomeres of the dividing egg, in which some parts of the outer layer have such a degree of viscosity that the segmenting cells remain united. The union of cells in resting tissues may be accomplished by means of secondary differentiations, which lead to the production of special structures. There is reason for believing that when, under the influence of certain stimuli these cells enter into the state of amœboid movement, these differentiations are at least partially lost and this implies a change in the condition of the outer layer of the cell, which exhibits amœboid movement and on which the agglutinability, and therefore stereotropism, depends.

Such changes in environment which lead to amœboid movement, alterations in consistency of protoplasm, stereotropic response, play a great part in pathological conditions, in inflammation, wound healing, and tumor growth, in all of which cellular stereotropic movements are a significant factor. Under natural conditions these movements occur not only during embryonic development in various types

of cells, but also in the adult organism, for instance in the ovary during atresia of the follicles, in the endothelial cells of the corpus luteum during the formation of blood vessels and in the lymphocytes migrating through epithelial surfaces.

It is possible further to analyse some of the factors and especially the significance of agglutination in the formation of certain tissue structures. In general, cell division not accompanied by amœboid movements tends to the production of epithelial surfaces. Tissues which show active amœboid and spreading out movements, may produce structures which differ according to the relative degree of agglutinability and energy of amœboid movement present. If the amœboid motility is very marked in proportion to the degree of adhesiveness, we tend to have tissues of a more or less loose character. Thus the fibroblasts are connected with each other through relatively small areas of contact, while they are sending out long pseudopodia and moving freely along solid bodies. In epithelial tissues, or in tissues of similar morphological character, the preponderance of amœboid motility over the adhesiveness of the cells is much less pronounced and these cells are therefore joined together in wider surfaces of contact and may form more or less connected layers. The same differences we find between the growth of sarcoma cells, which behave similarly to fibroblasts, and carcinoma cells which are epithelial in character. Great stickiness may lead to the formation of cell clumps, and if it is associated with a tendency to amœboid movement and spreading out of the adhesive cells, it may lead to the formation of tissue layers, in which strands of spread out cells form a net. This net formation is due to the fact that the cells move away from the cell clumps, which serve as centers, and form thus secondarily strands of spread out cells, which connect with each other.

In the process of tissue formation, such as we observe in tissue growing in culture media *in vitro*, two phenomena are noticeable in outgrowing cells, (1) the stereotropism, which leads the cells to grow in contact with solid surfaces, (2) the tendency of the cells to grow

out in a centrifugal direction away from the piece of tissue implanted; thus a more or less radial and often tree-like branching arrangement of the outgrowing cell strands is produced. We have discussed above the stereotropic response. The centrifugal arrangement can be conveniently studied in amœbocyte tissue. Several years ago we tested experimentally the possible significance of the galvanic current and differences in electric potential in the centrifugal direction of cell migration. Our results were negative, neither did the direction of light rays influence the movements. It is very probable that the centrifugal growth depends upon the following two factors, (1) the tendency of the cells adhering to each other to separate, to send out pseudopodia and to move in such a direction that two or more cells forming a clump become isolated, (2) the tendency of a healthy cell to continue for a certain time to form pseudopods at the same part of the cell at which this process has been induced. These two factors, the existence of which observation of the moving cells verifies, would be sufficient to produce the centrifugal movement, which would thus partly represent a statistical chance phenomenon. Inasmuch as the isolated cells and the cell clumps become less frequent with increasing distance from the central piece, this would insure a centrifugal, more or less net-like growth, or in other cases a tree-like growth, such as we found under various conditions. We may assume that the same factors play a role during the growth within the organism.

Tissue formation depends upon a combination of cell movements and cell divisions. We have seen that contact with a solid base is a prerequisite for the outgrowth of tissues; but in addition we found more recently that in various tissues growing in vitro, a very active mitotic cell division may be induced in favorable liquid culture media supplied with a sufficient amount of oxygen, even under conditions which do not permit an active outgrowth because of the lack of a solid surface along which the cells would be able to migrate.¹⁰

While it is thus possible to separate experi-

mentally mitotic cell proliferation and migration of cells in tissue cultures, the same stimulus usually tends to produce both of these reactions together. A suitable change in environmental conditions usually brings about alterations in the cells, which lead to both mitotic cell division and migration in tissues, provided they are capable of both of these activities. The difference in actual response on the part of different tissues depends upon the structure of the tissue, which enables certain kinds of cells to migrate very readily and to divide only with difficulty or not at all, and other tissues to divide much more readily than to make amœboid movements.

The stereotropic reaction of tissue cells to an environmental change consists of two component parts, (a) of amœboid movement and (b) of alterations in the consistency of the outer layer of the tissue cells; the latter change may vary very much in different cases. In some cases a previously non-sticky surface may become sticky as the result of the environmental change (as in amœbocytes, the free surface of endothelial cells, perhaps in lymphocytes and certain other cells), while in other cases a certain degree of usually circumscribed adhesiveness pre-existed, but became more general or stronger as the result of the environmental change.

These changes in motility and adhesiveness are responses of a living organism to a stimulus. This is quite apparent in the case of the amœbocytes and in the reactions of the experimental amœbocyte tissue, where a mechanical stimulus leads to that far going alteration in cell consistency, which makes possible both stereotropic reactivity and tissue formation; but in principle, conditions are similar also in the case of other tissues.

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THE SHENANDOAH CAVERNS

THE exhibition of caverns to the traveling public is noted by the United States Geological Survey as a growing industry in the Shenandoah Valley of Virginia. The famous Valley Pike, now a link in the New York to Atlanta highway, is traversed yearly by thousands of automobile tourists, and no one has adequately

¹⁰Leo Loeb and Moyer S. Fleisher, *Journ. Med. Research*, 1919, XL, 509.